REMARKS

Claim 4 is pending in the instant application. Claim 4 has been rejected. Claim 4 has been amended. Reconsideration is respectfully requested in light of the amendments and the following remarks.

I. Rejection of Claim 4 Under 35 U.S.C. 112, Second Paragraph

Claim 4 has been rejected under 35 U.S.C., second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner suggests that the claim recites "the actual picogram per milliliter of blood" in step (d) and this limitation lacks sufficient antecedent basis. Applicants have amended claim 4 to clarify the antecedent basis cited by the Examiner. Accordingly, the claim as amended meets the requirements of 35 U.S.C. 112, second paragraph, and withdrawal of this rejection is respectfully requested.

II. Rejection of Claim 4 Under 35 U.S.C. 102(e)

Claim 4 has been rejected under 35 U.S.C. 102(e) as being anticipated by Zoghbi et al. (US Patent Application

2004/0243010). The Examiner suggests that this reference discloses a method of determining the level of BNP in a sample from a patient prior to exercise to establish a baseline, and also determining the level of BNP in a sample from the patient post exercise, The Examiner suggests that the patent teaches that the levels of BNP are determined in pg/ml before and immediately after exercise of the patient and that the increase in the levels after exercise is 13.3 pg/ml, which is greater than 10 pg/ml. Applicants respectfully traverse this rejection.

Claim 4 as amended recites a method for detecting cardiac ischemia in an individual suspected of suffering from ischemic cardiovascular disease that comprises measuring actual picrogram per milliliter of blood levels of either BNP or NTproBNP in blood samples from an individual both before and after the individual has completed an exercise stress test with myocardial perfusion imaging wherein a dual isotope, rest-stress protocol is used, and then the active steps of determining an absolute level of change in the actual pg/ml of blood level of BNP or NTproBNP, as well as diagnosing cardiac ischemia by identifying the absolute level of change in the actual pg/ml of blood level of a peptide as being greater than 10 pg/ml of BNP or as being

greater than 5 pg/ml of NTproBNP. Applicants point out that data are provided showing that the method of the present invention is based on measurement of actual picrogram per milliliter of blood levels and that the changes in the blood levels after exercise relate to either the absolute level of change in the actual pg/ml of blood level of a peptide as being greater than 10 pg/ml of BNP or as being greater than 5 pg/ml of NTproBNP. Moreover, in Table 6, the data gathered using the method of the present invention are shown to be both sensitive and specific with a high level of diagnostic accuracy as compared in particular to ECG changes, with a BNP change of equal to 10 pg/ml being useful for diagnosis.

Zoghbi et al. (US2004/0243010) disclose use of an entirely different endpoint for assessing risk of ischemia in patients, including the method involving measurement of blood levels of BNP in the same patient both before and after exercise. As taught in Examples 5-7, and Table 1, pages 9-10 of the application, although BNP increased from baseline to immediately post-exercise in individuals with ischemia as well as those without ischemia, the actual pg/ml change in BNP levels post exercise in patients either with or without ischemia had a

median value of 15.5 pg/ml in ischemia patients, i.e., patients diagnosed with ischemia, and that the difference between the change in pg/ml of BNP between ischemic patients and those identified as being not ischemic was not statistically significant (p-value reported to be 0.115). Therefore, absolute levels of BNP in blood did not differ between such individuals (see paragraphs [0104] and [0105]). As stated in the previous replies (dated October 10, 2008 and may 21, 2009), the application states *"Neither the absolute BNP levels at peak nor the absolute level of rise from baseline to immediate post-exercise differentiated between ischemic and non-ischemic patients."* [see paragraph [0104]). Contrary to the Examiner's suggestion, this teaching is on point. This is because nowhere does this application teach or suggest the actual magnitude of changes in blood levels of BNP in any individual patients after exercise as compared to before exercise (*i.e.*, individual patient data are not provided). The values that the Examiner points to are mean values not individual patient values. The patent application teaches that what is important is the "percent increase in BNP" for any one individual or for any population. This is further illustrated in Example 6 on page 9

of the patent application where it is taught that the median baseline level of BNP in patients without ischemia was 15.01 pg/ml and immediately post-exercise in this group exhibited a median of 34.7 pg/ml. Thus, the application shows a median increase for the group of greater than 10 pg/ml, which was not different than the median increase in the patient group with ischemia (Example 7). This teaching by Zoghbi et al. is not the same as the method of claim 4 as amended which recites specifically identifying the actual increases in BNP or NTproBNP blood levels, in pg/ml, in a single individual, not a group of individuals and the mean for the group, and that this identification is diagnostic of cardiac ischemia. As a result, the application of Zoghbi teaches away from the method of the present invention which relies on measurement of actual levels of natriuretic peptides in blood, not percent increases as is used by Zoghbi et al. MPEP 2131 states that in order to anticipate an invention the cited reference must teach each and every limitation of the claims. As discussed *supra*, the cited reference fails to diagnose cardiac ischemia based on the use of actual picrogram levels of BNP or NTproBNP in blood. Accordingly, the reference fails to teach or suggest the

limitations of the claims as amended and withdrawal of this rejection is respectfully requested.

III. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

Jane Massey Licata

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Licata & Tyrrell P.C.
66 E. Main Street
Marlton, NJ 08053
856-810-1515
Email: jmlicata@licataandtyrrell.com